(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 467 331 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **02.11.95** (51) Int. Cl.[6]: **C07H 17/08**, A61K 31/71

(21) Application number: **91111948.5**

(22) Date of filing: **17.07.91**

(54) O-methyl derivatives of azithromycin A, process and intermediates for their preparation, and use thereof in the preparation of pharmaceuticals.

(30) Priority: **18.07.90 YU 1409/90**

(43) Date of publication of application:
22.01.92 Bulletin 92/04

(45) Publication of the grant of the patent:
02.11.95 Bulletin 95/44

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 307 128

JOURNAL OF ANTIBIOTICS, vol. 37, no. 2, February 1984, Japan Antibiotics Research Association, Tokyo (JP); S. MORIMOTO et al., pp. 187-189

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EP 0 467 331 B1

Description

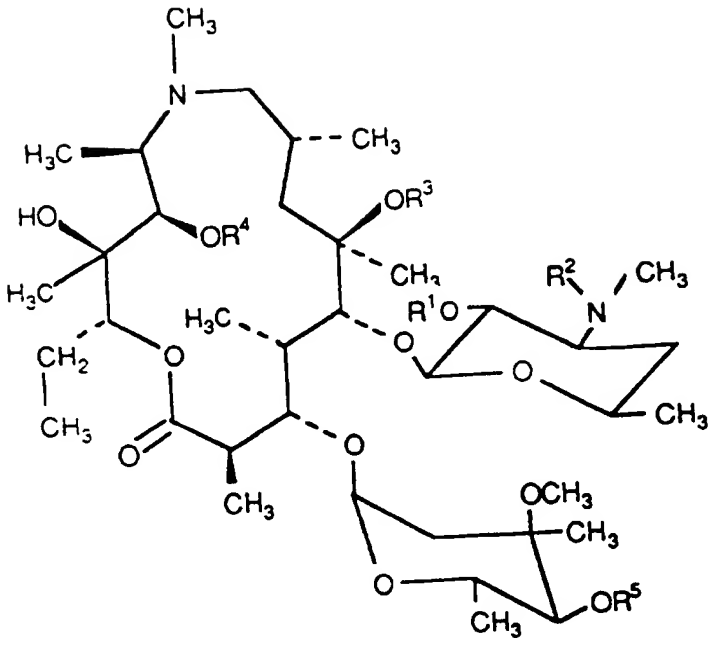
This invention relates to novel, semisynthetic macrolide antibiotics of the azalide series, particularly to O-methyl derivatives of azithromycin A and to pharmaceutically acceptable addition salts thereof, to a process and intermediates for the preparation thereof, and to their use in the preparation of pharmaceuticals, which are particularly indicated as antimicrobial agents.

Erythromycin A is a macrolide antibiotic, whose structure is characterized by a 14-membered aglicone ring, possessing a keto group in C-9 position (Bunch R.L. et al, US patent 2,653,899; 9/1953); it has been hitherto the leading macrolide antibiotic in the treatment of infections in humans. However, in acidic medium it is easily converted into anhydroerythromycin, which is an inactive C-6/C-12 metabolite of a spiroketal structure (Kurath P et al., Experientia 1971, 27 362). It has been known that the spiro-cyclisation of erythromycin A is successfully inhibited by means of a chemical transformation of C-9 ketone upon the obtaining of C-9 oximes (Djokić S. et al., Tetrahedron Lett., 1967, 1945) or C-9(R) and C-9(S) amines (Egan R.S. et al, J.Org.Chem., 1974, 39, 2492), or by the elimination of the C-9 ketone upon the expansion of the aglycone ring (Kobrehel G. et al., US patent 4,328,334; 5/1982). Thus Beckmann rearrangement of erythromycin A oxime, followed by the reduction of the obtained imino ether (Djokić S. et al, J.Chem.Soc.Perkin Trans 1, 1986, 1881) yielded the 11-aza-10-deoxo-10-dihydroerythomycin A (9-deoxo-9a-aza-9a-homoerythromycin A), which was the first 15-membered macrolide antibiotic of the azalide series. Upon methylation of the newly introduced secondary amino group in the aglycone ring with formaldehyde in the presence of formic acid *via* the modified Eschweiler-Clark procedure (Kobrehel G. and Djokić S., BE patent 892,357; 7/1982), or upon preliminary protection of the amino groups by means of conversion into the corresponding N-oxides, followed by the alkylation and reduction of the obtained N-oxides (Bright G., US patent 4,474,768; 10/1984), there was obtained the N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A) (IUPAC Nomenclature of Organic Chemistry, 1979, 68-70. 459, 500-503), which is being clinically tested under the non-proprietary name of azithromycin. In comparison with the parent antbiotic, azithromycin exhibits, in addition to an improved stability in acidic medium, also an improved *in vitro* activity against gram-negative microorganisms and a significantly higher conncentration in the tissues, and there is even being tested the possibility of a one-day dose (Ratshema J. et al, Antimicrob. Agents Chemother., 1987, 31, 1939).

Further, it has been known that the C-6/C-12 spiro-cyclisation of erythromycin A is successfully inhibited by means of O-methylation of the hydroxy group in C-6 position of the aglycone ring (Watanabe Y. et al., US patent 4,331,803; 5/1982). The reaction of erythromycin A with benzyl chloroformate, followed by the methylation of the obtained 2'-0,3'-N-bis(benzyloxycarbonyl)-derivative, upon the elimination of the protective groups in positions 2'- and 3'- as well as the N-methylation of the 3'-methylamino group under reductive conditions, yields, in addition to 6-O-methyl-erythromycin A, also significant quantities of 11-O-methyl- and 6,11-di-O-methyl-erythromycin A (Morimoto S. et al, J. Antibiotics 1984, 37, 187). A higher selectivity is achieved by the preliminary oximation of the C-9 ketones and the O-methylation of the corresponding substituted or unsubstituted benzyloximino derivatives (Morimoto S. et al, US patent 4,680,368; 7/1987). 6-O-methyl-erythromycin A is being clinically tested under the non-proprietary name of clarithromycin. In comparison to erythromycin A, clarithromycin exhibits an improved *in vitro* activity against gram-positive microorganisms (Kirist H.A. et al, Antimicrobial Agents and Chemother., 1989, 1419).

The Applicant's search has revealed no disclosure on O-methyl derivatives of azithromycin A in the State of the Art.

Hence the first object of the present invention are new O-methyl derivatives of azithromycin A of the formula (I)



I

wherein

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

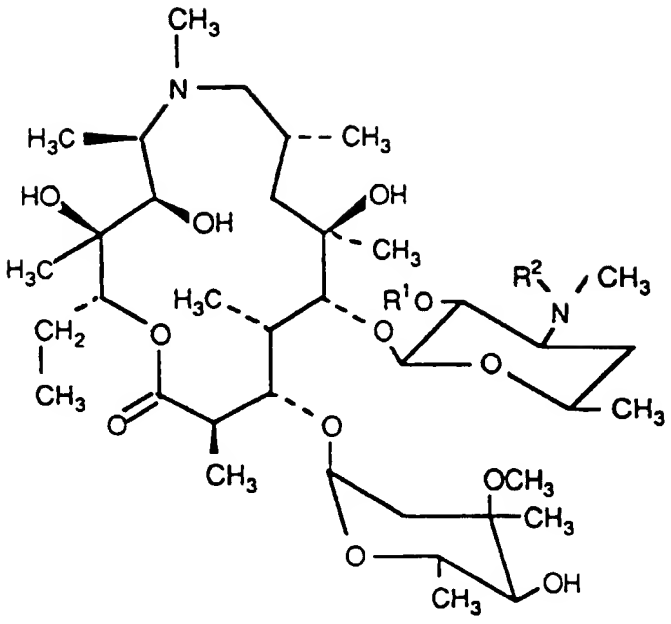
Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

and their pharmaceutically acceptable acid addition salts.

A further object of the present invention is a process for the preparation of O-methyl derivatives of azithromycin A of the formula (I) and of their pharmaceutically acceptable acid addition salts, wherein azithromycin or its dihydrate (Djokić S. et al, J. Chem. Research (S), 1988, 152-153; (M) 1988 1239-12621) of the formula (II)



II

wherein

IIa $R^1 = H, R^2 = CH_3$,

is reacted with benzyl chloroformate in the presence of an excess of a suitable base, e.g. sodium hydrogen carbonate, in a reaction inert solvent, e.g. benzene, at a temperature of 25 °C to 60 °C, within 3 to 24 hours, depending on the reaction temperature, followed by O-methylation of the hydroxy groups in the C-6, C-11 and C-4'' positions of a new, as yet undisclosed intermediate 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-azithromycin A of the formula (II),
wherein

IIb $R^1 = R^2 = CO_2CH_2C_6H_5$,

with a 1-18 molar excess of an appropriate methylation agent, e.g. methyl iodide, dimethyl sulfate, methyl methanesulfonate or methyl *p*-toluenesulfonate, in the presence of an appropriate base, e.g. sodium hydride, aqueous potassium hydroxide or sodium hydroxide, in an appropriate solvent, e.g. dimethyl sulfoxide or N,N-dimethyl-formamide, or their mixtures with a reaction inert solvent, e.g. tetrahydrofurane, acetonitrile, ethyl acetate, 1,2-dimethoxyethane, at a temperature of 0 °C to room temperature, within 3 to 30 hours, yielding a mixture of O-methyl-2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-azithromycin A of the formula (I),
wherein

Ia $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = CH_3, R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = CH_3, R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^5 = H, R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = R^5 = CH_3$

which is optionally subjected to

A) separation on a silica gel column (Silica gel 60, Merck Co., 70-230 mesh) with the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5), yielding chromatographically homogenous compounds (Ia) of an R_f 0.660, (Ib) of an R_f 0.811, (1c) of an R_f 0.843 and (Id) of an R_f 0.881, which are subsequently subjected to the elimination of the protecting benzyloxycarbonyl groups in positions 2'- and 3'- by means of

hydrogenolysis in a solution of lower alcohols, e.g. methanol or ethanol, in the presence of a catalyst, e.g. palladium black or palladium-on-carbon, in a hydrogen atmosphere at a pressure of 1-20 bar, under stirring of the reaction mixture, within 2-10 hours, at room temperature, yielding, upon filtration of the catalyst and the isolation of the product by means of conventional pH-gradient extraction methods (pH 5.0 and pH 9.0) from water with an appropriate hydrophobic solvent, e.g. chloroform, dichloromethane, ethyl acetate etc., the O-methyl-N-demethyl-azithromycin A derivatives of formula (I), wherein

Ie $R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$

If $R^1 = R^2 = R^5 = H, R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H, R^4 = CH_3$

Ih $R^1 = R^2 = H, R^3 = R^4 = R^5 = CH_3$

which are then subjected to reductive N-methylation of the 3'-methylamino group with 1-3 equivalents of formaldehyde (37%) in the presence of an equal or double quantity of formic acid (98-100%) or another hydrogen source, in a reaction inert solvent chosen from halogenated hydrocarbons, e.g. chloroform, or lower alcohols, e.g. methanol or ethanol, lower ketones, e.g. acetone, at reflux temperature of the reaction mixture within 2 to 8 hours, yielding upon the isolation of the product by means of conventional pH-gradient extraction methods (pH 5.0 and pH 9.0) O-methyl-azithromycin A derivatives of formula (I), wherein

Ii $R^1 = R^4 = R^5 = H, R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H, R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H, R^2 = R^4 = CH_3$

Il $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

or

B) elimination of the protecting benzyloxycarbonyl group in 2'- and 3'-positions by hydrogenolysis as described in A), yielding a mixture of 6-O-methyl- (Ie), 6,11-di-O-methyl- (If), 11-O-methyl- (Ig) and 6,11,4''-tri-O-methyl-N-demethyl-azithromycin A (Ih), which is subjected to reductive N-methylation with formaldehyde (37%) in the presence of formic acid (98-100%) or some other hydrogen source, as described in A), yielding a mixture of 6-O-methyl- (Ii), 6,11-di-O-methyl-(Ij), 11-O-methyl- (Ik) and 6,11,4''-tri-O-methyl-azithromycin A (Il), which is subjected to separation on a silica gel column with the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5), yielding chromatographically homogenous (TLC, the same solvent system) O-methyl derivatives of azithromycin A (Ii) of an R_f 0.346, (Ij) of an R_f 0.393, (Ik) of an R_f 0.428 and (Il) of an R_f 0.456.

Pharmaceutically acceptable addition salts of the compounds of formula (I) are obtainable by reacting O-methyl derivatives of azithromycin A (I) with at least an equimolar quantity of a corresponding organic or inorganic acid, chosen e.g. from hydrogen chloride, hydrogen iodide, sulphuric acid, phosphoric acid, acetic acid, propionic acid, trifluoroacetic acid, maleic acid, citric acid, ethyl succinic acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, lauryl- sulfonic acid and the like, in a reaction inert solvent. The addition salts are isolated by filtration if they are insoluble in the applied reaction inert solvent, or by precipitation by means of a non-solvent, most often by means of a lyophilization procedure.

O-methyl derivatives of azithromycin A of the formulae (Ii)-(Il) and their pharmaceutically acceptable addition salts have a potent antimicrobial activity. The preliminary antibacterial *in vitro* activity of 6-O-methyl-azithromycin A (Ii) was determined on a series of gram-positive and gram-negative test bacteria and clinical isolates in comparison with erythromycin A. The assessment was performed by the "tube dilution" method. In the investigation there were used 24-hours cultures in "brain hearth bouillon " of standard strains and freshly isolated strains from a clinical sample. The results are expressed as Minimal Inhibitory Concentration or Bactericidal Concentration (MIC and MBC resp. in μg/mL) and represented in Tables 1 and 2, and they show that 6-O-methyl-azithromycin A has a somewhat improved activity on the investigated strains in comparison with erythromycin A.

In Table 3 there are represented *in vitro* tests of 6-O-methyl- (Ii), 6,11-di-O-methyl- (Ij), 11-O-methyl- (Ik) and 6,11,4''-tri-O-methyl-azithromycin A (Il) in comparison with azithromycin. Minimal Inhibitory Concentrations (MIC; µg/mL) determined on a series of standard bacterial strains show that 6-O-methyl-azithromycin A (Ii) is twice as active on *Bacillus subtilis* NCTC 8241 and *Sarcina lutea* ATCC 9341, and four times as active on *Micrococcus flavus* ATCC 6538 P with respect to azithromycin. A significantly higher activity was also exhibited by 11-O-methyl-azithromycin A (Ik). Namely, the majority of the investigated bacterial strains was 2 to 4 times more sensitive in comparison with the parent antibiotic.

It is a further object of the present invention to provide pharmaceuticals comprising an effective, yet physiologically acceptable dose of the novel compounds of the present invention. Compounds (Ii)-(Il) as well as their pharmaceutically acceptable salts may be used as therapeutical agents in the treatment of human or animal infectious diseases caused by gram-positive bacteria, mycoplasmas or patogenous bacteria, which are sensitive to compounds (Ii)-(Il). Thus, the compounds (Ii)-(Il) and their pharmaceutically acceptable addition salts may be administered orally or parenterally, e.g. in the form of *s.c.* or *i.m.* injections, tablets, capsules, powders and the like, formulated in accordance with the conventional pharmaceutical practice.

TABLE 1

Antibacterial *in vitro* activity of 6-O-methyl-azithromycin A (Ii) in comparison with erythromycin A

Test Organism	Erythromycin A		6-O-methyl-azithromycin A (Ii)	
	MIC	MBC	MIC	MBC
Staphilococcus aureus ATCC 6538-P	0.2	0.8	0.2	0.4
Streptococcus faecalis ATCC-8043	0.2	0.8	0.2	0.4
Sarcina lutea ATCC-9341	0.2	0.4	0.1	0.2
Escherichia coli ATCC 10536	50	>50	1.6	3.2
Klebsiella pneumoniae NCTC-10499	>50	>50	12.5	50
Pseudomonas aeruginosa NCTC-10490	>50	>50	>50	>50

Substrate: Brain hearth bouillon
Incubation: 24 hours, 37 °C
MIC: Minimal Inhibitory Concentration (µg/mL)
MBC: Minimal Bactericidal Concentration (µg/mL)

TABLE 2

Antibacterial *in vitro* activity of 6-O-methyl-azithromycin A (Ii) in comparison with erythromycin A against clinical isolates				
Test Organism	Erythromycin A		6-O-methyl-azithromycin A (Ii)	
	MIC	MBC	MIC	MBC
Staphylococcus aureus 10099	0.1	0.2	0.05	0.1
Staphylococcus saprophyticus 3947	0.4	0.8	0.4	0.8
Streptococcus faecalis 10390	0.8	3.1	0.8	3.1
Staphylococcus aureus 10097	0.1	0.4	0.05	0.4
Streptococcus pneumoniae 4050	0.1	0.4	0.025	0.1
Haemophylus influenzae 4028	0.05	0.2	0.05	0.2
Substrate: Brain hearth bouillon Incubation: 24 hours, 37 °C MIC: Minimal Inhibitory Concentration (µg/mL) MBC: Minimal Bactericidal Concentration (µg/mL)				

TABLE 3

Antibacterial *in vitro* activity of the novel O-methyl-azithromycin A derivatives in comparison with azithromycin					
Test Strain	MIC (µg/mL)				
	(IIa)	(Ii)	(Ij)	(Ik)	(Il)
Micrococcus flavus ATCC 6538P	1.56	0.39	1.56	0.2	3.125
Corynebacterium xerosis NCTC 9755	6.25	12.5	12.5	1.56	25.0
Staphylococcus aureus ATCC 10240	0.39	0.79	0.78	0.1	3.125
Bacillus subtilis NCTC 8241	0.39	0.2	0.78	0.1	3.125
Bacillus pumilus NCTC 8241	0.2	0.2	0.78	0.05	3.125
Bacillus cereus NCTC 10320	0.39	0.78	1.56	0.1	3.125
Sarcina lutea ATCC 9341	0.05	0.0125	0.05	0.0125	0.05
Staphylococcus epidermidis ATCC 12228	0.1	0.1	1.56	0.1	3.125
Staphylococcus faecalis ATCC 8043	0.05	0.05	0.78	0.05	0.78
Pseudomonas aeruginosa NCTC 10490	100.0	100.0	100.0	25.0	200.0
Escherichia coli ATCC 10536	0.78	3.125	6.25	0.78	6.25
Substrate: Brain hearth Bouillon Incubation: 24-48 hours, 37 °C Inocculum; 10^{-5}-10^{-6} cfu/mL					

The invention is illustrated by the following Examples.

EXAMPLE 1

2'-0,3'-N-Bis(benzyloxycarbonyl)-N-demethyl-azithromycin A (IIb)

Method A

Upon the addition of $NaHCO_3$ (48g) into a solution of azithromycin dihydrate (30g; 0.038 mole) in 140 mL of dry benzene the reaction mixture was heated under stirring to 55-60 °C, whereupon there were added drop by drop gradually within 1 hour 75 mL (89.63 g; 0.53 mole) of benzyl chloroformate. The reaction mixture was kept stirring at this temperature for 3 hours and left standing overnight at room temperature. The benzene suspension was extracted three times with 150 mL of 0.25 N HCl, the benzene solution was dried over $CaCl_2$, filtered, and evaporated at reduced pressure into a thick oil. The obtained residue was added drop-by-drop under thorough stirring into 500 mL of cooled petrolether, the reaction suspension was stirred under cooling for 4 hours, the precipitate was filtered, washed with petroleum ether and dried, yielding 27.5 g (71.6%) of the title product, which upon recrystallization from ether/petroleum ether yielded a product of a m.p. 148-154 °C.
EI-MS m/s 1003 (M^+)
TLC, $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5) R_f 0.704
IR ($CHCl_3$): 3510, 3350, 2960, 1740, 1690, 1605, 1450, 1380, 1330, 1290, 1255, 1160, 1115, 1050, 995 cm^{-1}.
^1H NMR ($CDCl_3$): 2.301 (3H, 9a-NCH_3), 2.844, 2.802 (3H, 3'-NCH_3), 3.397 (3H, 3''-OCH_3).
^{13}C NMR ($CDCl_3$): 177.260 (C-1), 100.115 (C-1'), 95.149 (C-1''), 75.028 (C-6), 74.607 (C-12), 69.415 (C-9), 64.617 (C-10), 36.964 (9a-NCH_3) and 26.016 (C-8) ppm.

Method B

Upon the addition of $NaHCO_3$ (22 g) under stirring into a solution of benzyl chloroformate (30mL; 0.21 mole) in 50 mL of dry benzene, there were added gradually within 3 hours 15 g (0.019 mole) of azithromycin. At the moment of the addition of about 3/4 of the total amount of azithromycin, there was added a further quantity of 15 mL (0.106 mole) of benzyl chloroformate. The reaction mixture was kept under stirring for 24 hours at room temperature, filtered, whereupon the filtrate was extracted three times with 150 mL of 0.25 N HCl, dried over $MgSO_4$, and evaporated at reduced pressure. Upon the addition of petroleum ether the crude 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-azithromycin A was precipitated, the obtained precipitate was filtered and immediately suspended under stirring in 50 mL of cold ether. The reaction suspension was stirred at room temperature for 1 hour, the precipitate was filtered and dried, yielding 8.67 g (43.09%) of a homogeneous product (TLC) of identical physical- chemical characteristics as cited above in Method A).

EXAMPLE 2

O-Methylation of 2'-0,3'-N-bis(benzyloxycarbonyl)-N-demethyl-azithromycin A (Ia), (Ib), (Ic) and (Id)

Method A

Upon the addition of methyl iodide (6 mL; 0.106 mole) into a solution of the product of Example 1 (6 g; 0.006 mole) in 64 mL of dimethyl sulfoxide and tetrahydrofurane (1:1), there were added methyl iodide (6.6 mL; 0.106 mole) and then, gradually within 4 hours at room temperature, 2.4 g (approx. 0.06 mole) of NaH (55-60%) in oil. The reaction suspension was stirred for further 5 hours, left standing overnight, poured into a saturated NaCl solution (100 mL), and extracted twice with 100 mL of ethyl acetate. The combined organic extracts were washed three times with 100 mL of saturated NaCl solution, dried over K_2CO_3, and evaporated, yielding 6.35 g of a crude product, which was subjected to hydrogenolysis in accordance with the process described in Example 9 or, optionally, to purification by means of chromatography on a silica gel column (Silica gel 60, Merck Co., 70-230 mesh), using the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5).

From 1.5 g of the crude product there were obtained, upon the concentration and evaporation of the fractions of R_f 0.881 (TLC; identical solvent system), 0.12 g of the chromatographically pure 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-6,11,4''-tri-O-methyl-azithromycin A (Id):
^1H NMR ($CDCl_3$): 2.246 (3H, 9a-NCH_3), 2.831, 2.798 (3H, 3'-NCH_3), 3.367 (3H, 3''-OCH_3), 3.305 (3H, 6-

OMe), 3.465 (3H, 4"-OCH_3), and 3.485 (3H, 11-OCH_3) ppm.
^{13}C NMR ($CDCl_3$): 176.975 (C-1), 69.920 (C-9), 35.967 (9a-NCH_3), 79.1 (C-6). 52.8 (6-OCH_3), 89.0 (C-11), 62.0 (11-OCH_3). 87.357 (C-4"), 61.131 (4"-OCH_3), 49.176 and 49.526 (3"-OCH_3) and 36.457 (3'-NCH_3) ppm.

Upon the combination and evaporation of the fractions of R_f 0.843, 0.32g of the chromatographycally pure 2'-0,3'-N-bis(benzyloxycarbonyl)-N-demethyl-11-O-methyl-azithromycin A (Ic) were obtained:
EI-MS m/s 1016 (M^+)
^1H NMR ($CDCl_3$): 2.239 (3H, 9a-NCH_3), 2.805, 2.847 (3H, 3'-NCH_3), 3.374 (3H, 3"-OCH_3), and 3.573 (3H, 11-OCH_3) ppm.

Upon the evaporation of the fractions of R_f 0.811, 0.316g of 2'-0,3'-N-bis(benzyloxycarbonyl)-N-demethyl-6,11-di-O-methyl-azithromycin A (Ib) were obtained:
IR ($CHCl_3$): 3570, 3490, 1740, 1690, 1455, 1380, 1330, 1295, 1260, 1200, 1160, 1120, 1095, 1055, 1005, 990, 980 cm^{-1}.
^1H NMR ($CDCl_3$): 2.292 (3H, 9a-NCH_3), 2.838, 2.795 (3H, 3'-NCH_3), 3.380 (6H, 6-OCH_3 and 3"-OCH_3) and 3.488 (3H, 11-OCH_3) ppm.
^{13}C NMR ($CDCl_3$): 177.939 (C-1), 69.471 (C-9), 35.271 (9a-NCH_3), 88.994 (C-11), 52.892 (6-OCH_3), 61.09 (11-OCH_3), 36.851 (3'-NCH_3), and 49.549, 49.154 (3"-OCH_3) ppm.

Upon concentration and evaporation to dryness of the fractions of R_f 0.661, 0.384 g of 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-6-O-methyl-azithromycin A (Ia) were obtained:
EI-MS m/s 1016 (M^+)
IR ($CHCl_3$): 3570, 3500, 2960, 2920, 1740, 1690, 1450, 1380, 1325, 1290, 1255, 1200, 1160, 1120, 1050, 995 cm^{-1}.
^1H NMR ($CDCl_3$): 2.288 (3H, 9a-NCH_3), 2.805, 2.847 (3H, 3'-NCH_3), 3.380 (6H, 6-OCH_3 and 3"-OCH_3) ppm.
^{13}C NMR ($CDCl_3$): 177.764 (C-1), 69.850 (C-9), 34.851 (9a-NCH_3), 78.106 (C-6), 74.661 (C-11),, 73.873 (C-12), and 52.822 (6-OCH_3) ppm.

Method B

Into a solution of the product of Example 1 (6 g) in 60 mL of dimethyl sulfoxide and tetrahydrofurane (1:1), there was added, under stirring, gradually within 2 hours at a temperature of 0-5 °C methyl iodide (3 mL) and 2.1 g of NaH (55-60%). The reaction mixture was stirred for 1 hour at 0-5 °C, the suspension was poured on a saturated NaCl solution and extracted with ethyl acetate. The organic extracts were washed with a saturated NaCl solution, dried over K_2CO_3, and evaporated to dryness at reduced pressure. The obtained product (2 g) was subjected to purification by means of chromatography on a silica gel column, using the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1.5) and yielding 0.89 g of 6-O-methyl derivative (Ia), 0.11 g of 6,11-di-O-methyl derivative (Ib) and 0.48 g of 11-O-methyl derivative (Ic).

Method C

Upon the addition of methyl iodide (6 mL) into a solution of the product of Example 1 (6 g) in 60 mL of N,N-dimethylformamide, there were added, under stirring, gradually within 2 hours at room temperature 2.4 g of NaH (55-60%). The reaction mixture was stirred for further 2 hours at said temperature and left overnight. Upon the isolation of the product in accordance with the procedure described in Method A), there were obtained 4.54 g of a mixture of 6,11-di-O-methyl derivative (Ib) and 6,11,4"-tri-O-methyl derivative (Id). This mixture was subjected to hydrogenolysis in methanol (60 mL) in the presence of a NaOAc/HOAc buffer (pH 5) and palladium-on-carbon (2g; 5%) as catalyst, according to the procedure described in Example 3.

Upon the isolation of the product and evaporation of the solvent at pH 9.0 there was isolated a mixture (2.33g) of 6,11-di-O-methyl-N-demethyl-azithromycin A (If) of R_f 0.220 and 6,11,4"-tri-O-methyl-N-demethyl-azithromycin A (Ih) of R_f 0.263, which upon separation on a silica gel column in the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1), yielded a chromatographically homogeneous product (If) and (Ih).

EXAMPLE 3

6-O-Methyl-N-demethyl-azithromycin A (Ie)

2.0 g (0.002 mole) of 2'-0,3'-N-bis(benzyl-oxycarbonyl)-N-demethyl-6-O-methyl-azithromycin A (Ia) were dissolved in 30 mL of ethanol. 10 mL of water, which contained 0.185 mL of acetic acid and 0.3g of sodium acetate (pH 5) and 0.7g of palladium-on-carbon (10%) was charged into the solution. The reaction mixture

was stirred under hydrogen pressure (10 bar) for 10 hours, the catalyst was filtered and evaporated to dryness. The residue was dissolved in $CHCl_3$ (30 mL) and upon the addition of water (30 mL) and adjustment of the pH of the reaction mixture with 1N HCl to 5.0, the layers were separated and the aqueous layer was extracted twice with $CHCl_3$ (each time with 15 mL).

To the reaction mixture $CHCl_3$ (30 mL) was added, the pH was adjusted to 9.0 under stirring with 2N NaOH, the layers were separated, and the aqueous layer was again extracted twice with $CHCl_3$ (each time with 15 mL). The combined organic extracts (pH 9.0) were dried over K_2CO_3, filtered and evaporated to yield 1.03 g (70%) of the title product:
EI-MS m/s 748
TLC, R_f 0.182
IR ($CHCl_3$): 3670, 3500, 2960, 2920, 1725, 1460, 1375, 1345, 1320, 1280, 1260, 1165, 1120, 1085, 1045, 1010, 995, 900 cm^{-1}.
^1H NMR ($CDCl_3$): 2.278 (3H, 9a-NCH_3), 2.406 (3H, 3'-NCH_3), 3.312 (3H, 3''-OCH_3), 3.384 (3H, 6-OCH_3) ppm.

EXAMPLE 4

6,11-Di-O-Methyl-N-demethyl-azithromycin A (If)

In accordance with the procedure of Example 3, from 0.165 g (0.16 mole) of 2'-0,3'-N-bis- (benzyloxycarbonyl)-N-demethyl-6,11-di-O-methyl-azithromycin A (Ib) by means of hydrogenolysis with palladium-on-carbon (10%) in ethanol in the presence of the buffer sodium acetate/acetic acid (pH 5.0), there were obtained 0.093 g (76,2%) of the chromatographically homogeneous title product; m.p. 95-98 °C.
EI-MS m/s 762
TLC, R_f 0.331
^1H NMR ($CDCl_3$): 2.265 (3H, 9a-CH_3), 2.422, (3H, 3'-NCH_3), 3.312 (3H, 3''-OCH_3), 3.374 (3H, 6-OCH_3) and 3.521 (3H, 11-OCH_3) ppm.
^{13}C NMR ($CDCl_3$): 177.7 (C-1), 65.9 (C-9), 36.8 (9a-NCH_3), 79.3 (C-6), 88.9 (C-11), 52.7 (6-OCH_3), 62.0 (11-OCH_3), 33.1 (3'-NCH_3), and 49.7 (3''-OCH_3) ppm.

EXAMPLE 5

11-O-Methyl-N-demethyl-azithromycin A (Ig)

In accordance with the procedure of Example 3, from 0.250 g (0.246 mmole) of 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-11-O-methyl-azithromycin A (Ic) by means of hydrogenolysis with palladium-on-carbon (10%) in methanol in the presence of the buffer sodium acetate/acetic acid (pH 5.0), there were obtained 0.168 g (89,5%) of 11-0-methyl-N-demethyl-azithromycin A (Ig):
TLC, R_f 0.244
IR ($CDCl_3$): 3500, 2970, 2940, 1736, 1460, 1380, 1165 cm^{-1}.
^1H NMR ($CDCl_3$): 2.44 (3H, 9a-NCH_3), 2.458, (3H, 3'-NCH_3), 3.336 (3H, 3''-OCH_3) and 3.590 (3H, 11-OCH_3) ppm.
^{13}C NMR ($CDCl_3$): 177.6 (C-1), 70.7 (C-9), 35.8 (9a-NCH_3), 74.4 (C-6), 85.0 (C-11), 62.7 (11-OCH_3), 36.7 (3'-NCH_3), and 49.4 (3''-OCH_3) ppm.

EXAMPLE 6

6-O-Methyl-azithromycin A (Ii)

Method A

Into a solution of 0.78 g (0.00104 mole) of 6-O-Methyl-N-demethyl-azithromycin A (Ie) in $CHCl_3$ (50 mL) there were added 0.085 mL (0.00113 mole) of formaldehyde (37%) and 0.078 mL (0.00203 mole) of formic acid (98-100%). The reaction mixture was stirred under reflux for 8 hours, cooled to room temperature, and poured onto 50 mL of water. Upon the adjustment of the pH of the reaction mixture with 1N HCl to 5.0, the layers were separated and the aqueous layer was extracted twice with $CHCl_3$ (each time with 20 mL). To the aqueous portion $CHCl_3$ (20 mL) was added, the pH was adjusted to 9.0 under stirring with 2N NaOH, the layers were separated, and the aqueous layer was again extracted twice with $CHCl_3$ (each time with 20

mL). The combined $CHCl_3$ extracts (pH 9.0) were dried over K_2CO_3 and evaporated to yield 0.495 g (62,74%) of the title product, which was optionally purified by chromatography on a silica gel column, using the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5) and yielding chromatographically homogeneous (Ii), m.p. 103-109 °C.

EI-MS m/s 762

TLC, R_f 0.346

IR (KBr): 3500, 2980, 2940, 1740, 1462, 1385, 1330, 1280, 1260, 1170, 1112, 1059, 1018, and 1055 cm^{-1}.

^1H NMR ($CDCl_3$): 2.300 (3H, 9a-NCH_3), 2.316 (6H, 3'-$N(CH_3)_2$), 3.333 (3H, 3"-OCH_3) and 3.384 (3H, 6-OCH_3) ppm.

^{13}C NMR ($CDCl_3$): 177.540 (C-1), 68.850 (C-9), 36.8 (9a-NCH_3), 79.2 (C-6), 52.822 (6-OCH_3), 61.627 (C-10), 40.350 (3'-$N(CH_3)_2$) and 49.457 (3"-OCH_3) ppm.

Biological activity: 1 mg contains 754 μg of azithromycin.

Method B

Into a solution of 0.5 g (0.668 mmole) of 6-O-methyl-N-demethyl-azithromycin A in acetone (30 mL) there were added 0.128 mL (1.71 mmole) of formaldehyde (37%) and 0.118 mL (3.06 mmole) of formic acid (98-100%), and it was refluxed under stirring for 2 hours. The reaction mixture was cooled to room temperature and acetone was evaporated to yield a thick syrup and upon addition of 20 mL of water the product was isolated by means of gradient pH extraction by means of methylene chloride as described in Method A). Yield: 0.46 g (90.3%).

EXAMPLE 7

6,11-Di-O-Methyl-azithromycin A (Ij)

In accordance with the procedure of Example 6, from 0.49 g (6.43 mmole) of 6,11-di-O-methyl-N-demethylazithromycin A (If) by means of reductive N-methylation with formaldehyde (37%; 0.083 mL) in the presence of formic acid (98-100%), there were obtained 0.46 g (92,3%) of the title product:

EI-MS m/s 776 (M^+)

TLC, R_f 0.391

^1H NMR ($CDCl_3$): 2.295 (3H, 9a-NCH_3), 2.316 (6H, 3'-$N(CH_3)_2$), 3.321 (3H, 3"-OCH_3) 3.38 (3H, 6-OCH_3) and 3.524 (3H, 11-OCH_3) ppm.

^{13}C NMR ($CDCl_3$): 177.540 (C-1), 68.237 (C-9), 36.739 (9a-NCH_3), 88.112 (C-11), 52.653 (6-OCH_3) and 61.852 (11-OCH_3) ppm.

EXAMPLE 8

11-O-Methyl-azithromycin A (Ik)

In accordance with the procedure of Example 6, from 0.32 g (0.43 mmole) of 11-O-methyl-N-demethyl-azithromycin A (Ig) by means of reductive methylation with formaldehyde (37%) in the presence of formic acid (98-100%), there were obtained 0.238 g (72,44%) of the title 11-O-methyl derivative (Ik):

EI-MS m/s 762 (M^+)

TLC, R_f 0.428

IR (KBr): 3510, 2975, 2940, 1738, 1460, 1350, 1165, 1054 cm^{-1}.

^1H NMR ($CDCl_3$): 2.246 (3H, 9a-NCH_3), 2.307 (6H, 3'-$N(CH_3)_2$), 3.352 (3H, 3"-OCH_3) and 3.591 (3H, 11-OCH_3) ppm.

EXAMPLE 9

6-O-Methyl-azithromycin A (Ii), 6,11-di-O-methyl-azithromycin A (Ij), 11-O-methyl-azithro- mycin A (Ik) and 6,11,4"-tri-O-methyl-azithromycin A (Il)

1) Into a solution of 2.16 g of the crude product of Example 2 in 30 mL of ethanol, there were added 10 mL of water containing 0.185 mL of acetic acid and 0.3 g of sodium acetate and 0.7 g of palladium-on-carbon (10%), whereupon the reaction mixture was subjected to hydrolysis, as described in Example 3. At a pH of 9.0 there were obtained 0.98 g of a mixture of 6-O-methyl- (Ie), 6,11-di-O-methyl- (If), 11-O-

methyl- (Ig), and 6,11,4"-tri-O-methyl-N- demethyl-azithromycin A (Ih).

2) Upon the dissolving of 0.98 g of the mixture obtained as described in (1), in $CHCl_3$ (50 mL), there were added 0.106 mL of formaldehyde (37%) and 0.096 mL of formic acid (98-100%) and it was subjected to N-methylation as described in Example 6. At a pH of 9.0 there were isolated 0.537 g of a mixture, which was subjected to chromatography on a silica gel column (Silica gel 60, Merck Co., 70-230 mesh), using the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1.5), and yielding 0.238 g of a chromatographically homogeneous (Ii) of R_f 0.346, 0.065 g of (Ij) of R_f 0.391, 0.105 g (Ik) of R_f 0.428 and 0.094 g (Il) of R_f 0.456.

EXAMPLE 10

6,11,4"-Tri-O-Methyl-N-demethyl-azithromycin A (Ih)

In accordance with the procedure of Example 3, from 3.35 g (3.21 mmole) of 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-6,11,4"-tri-O-methyl-azithromycin A (Id) by means of hydrogenolysis with palladium-on-carbon (10%; 1g) in ethanol (50mL) in the presence of the buffer sodium acetate/acetic acid (pH 5.0), there were obtained 1.41 g (56,7%) of the title product, which was optionally subjected to chromatography on a silica gel column using the solvent system $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:0.5), and yielding a TLC homogeneous product (Ih):

EI-MS m/s 775

TLC, R_f0.263

^1H NMR ($CDCl_3$): 2.262 (3H, 9a-NCH_3), 2.393 (3H, 3'-NCH_3), 3.308 (6H, 3"-OCH_3 and 6-OCH_3), 3.475 (4"-OCH_3) and 3.521 (11-OCH_3) ppm.

^{13}C NMR ($CDCl_3$): 175.0 (C-1), 64.8 (C-9), 79.8 (C-6), 50.6 (6-OCH_3) 86.1 (C-11), 59.1 (11-OCH_3), 87.7 (C-4") and 60.9 (4"-OCH_3) ppm.

EXAMPLE 11

6,11,4"Tri-O-Methyl-azithromycin A (Il)

In accordance with the procedure of Example 6, from 1.2 g (1.55 mmole) of 6,11,4"-tri-O- methyl-N-demethyl-azithromycin A (Ih), 0.131 mL of formaldehyde (37%; 1.71 mmole) and 0.121 mL (3.15 mmole) of formic acid (98-100%), there were obtained 0.75g (64,4%) of the title product.

EI-MS m/s 789

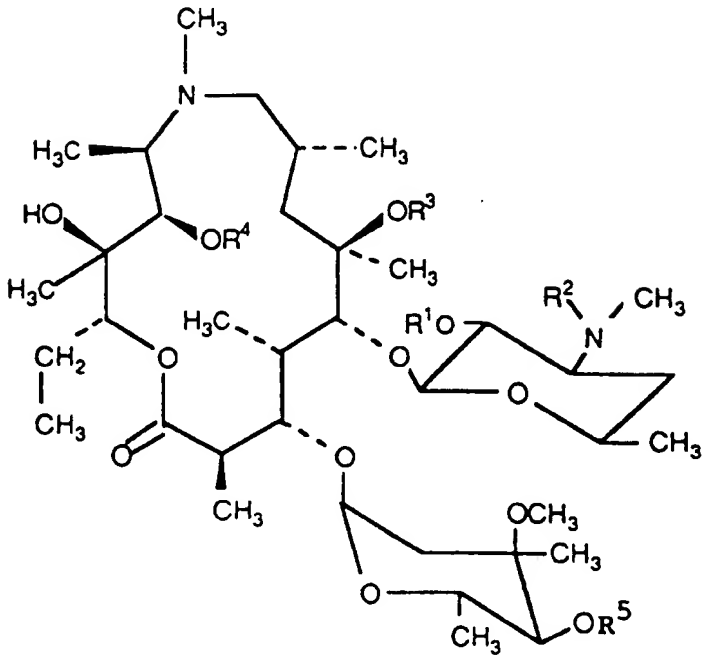
TLC, R_f0.456

^1H NMR ($CDCl_3$): 2.216 (3H, 9a-NCH_3), 2.311 (6H, 3'-$N(CH_3)_2$), 3.321 (3H, 3"-OCH_3), 3.302 (6-OCH_3), 3.482 (4"-OCH_3) and 3.521 (11-OCH_3) ppm.

^{13}C NMR ($CDCl_3$): 177.859 (C-1), 68.6 (C-9), 36.8 (9a-NCH_3), 80.7 (C-6), 51.0 (6-OCH_3), 89.0 (C-11), 62.0 (11-OCH_3), 87.3 (C-4") and 61.3 (4"-OCH_3) ppm.

Claims

1. O-methyl derivatives of azithromycin A of the formula (I)



(I)

wherein

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

and their pharmaceutically acceptable addition salts with inorganic or organic acids.

2. Substance as claimed in claim 1, characterized in that R^1 and R^2 are identical and stand for a benzyloxycarbonyl group, R^3 is CH_3, whereas R^4 and R^5 stand for hydrogen.

3. Substance as claimed in claim 1, characterized in that R^1 and R^2 are identical and stand for a benzyloxycarbonyl group, R^3 and R^4 are CH_3, whereas R^5 stands for hydrogen.

4. Substance as claimed in claim 1, characterized in that R^1 and R^2 are identical and stand for a benzyloxycarbonyl group, R^3 and R^5 are hydrogen, whereas R^4 stands for CH_3.

5. Substance as claimed in claim 1, characterized in that R^1 and R^2 are identical and stand for a benzyloxycarbonyl group, whereas R^3, R^4 and R^5 are CH_3.

6. Substance as claimed in claim 1, characterized in that R^1, R^2, R^4 and R^5 are identical and stand for hydrogen, whereas R^3 stands for CH_3.

7. Substance as claimed in claim 1, characterized in that R^1, R^2, and R^5 are identical and stand for hydrogen, whereas R^3 and R^4 stand for CH_3.

8. Substance as claimed in claim 1, characterized in that R^1, R^2, R^3 and R^5 are identical and stand for hydrogen, whereas R^4 stands for CH_3.

9. Substance as claimed in claim 1, characterized in that R^1 and R^2 are identical and stand for hydrogen, whereas R^3, R^4 and R^5 stand for CH_3.

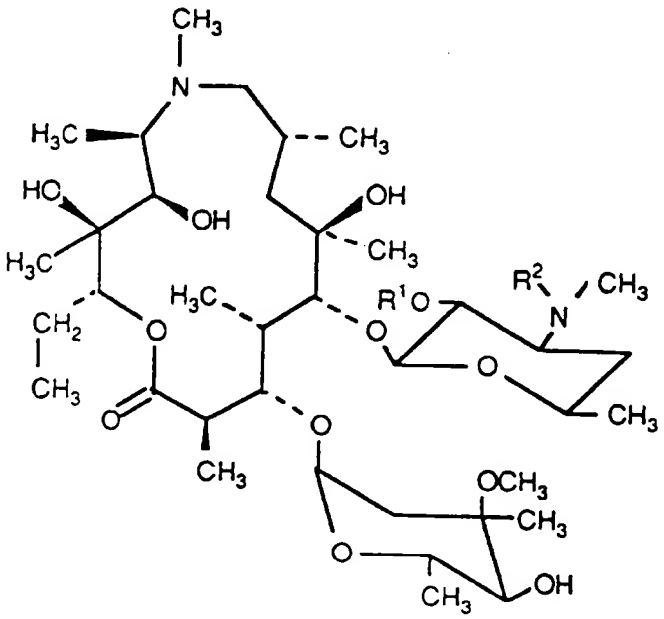
10. Substance as claimed in claim 1, characterized in that R^1, R^4, and R^5 are identical and stand for hydrogen, whereas R^2 and R^3 stand for CH_3.

11. Substance as claimed in claim 1, characterized in that R^1 and R^5 are identical and stand for hydrogen, whereas R^2, R^3 and R^4 stand for CH_3.

12. Substance as claimed in claim 1, characterized in that R^1, R^3, and R^5 are identical and stand for hydrogen, whereas R^2 and R^4 stand for CH_3.

13. Substance as claimed in claim 1, characterized in that R^1 stands for hydrogen, whereas R^2, R^3, R^4 and R^5 are identical and stand for CH_3.

14. Substance of formula (II)

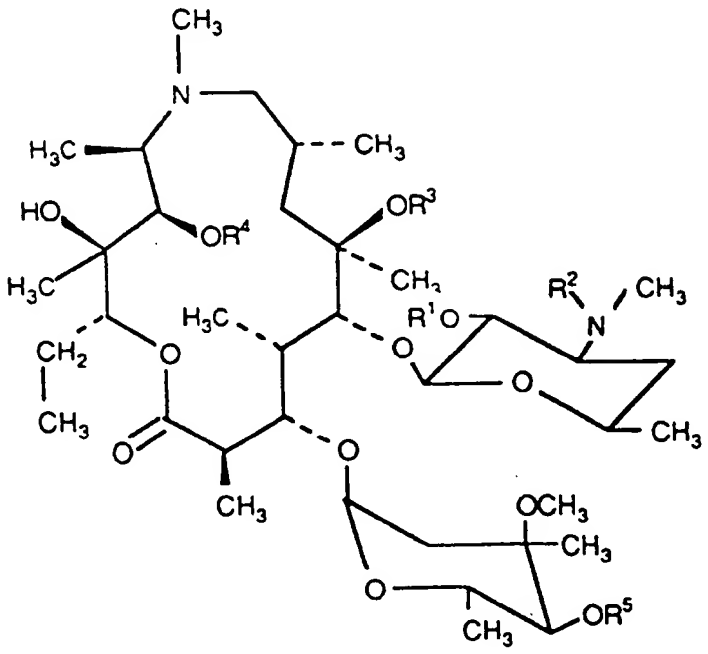


(II)

wherein

(IIb) $R^1 = R^2 = CO_2CH_2C_6H_5$.

15. A process for the preparation of O-methyl derivatives of azithromycin A of the formula (I)



(I)

wherein

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

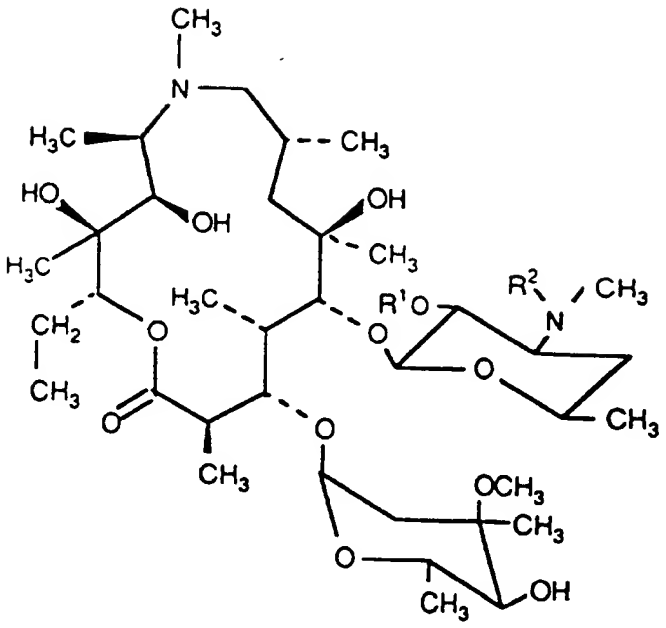
Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

and of their pharmaceutically acceptable acid addition salts, characterized in that azithromycin or its dihydrate of the formula (II)



(II)

wherein

IIa $R^1 = H, R^2 = CH_3,$

is reacted with benzyl chloroformate in the presence of an excess of a suitable base, e.g. sodium hydrogen carbonate, in a reaction inert solvent, e.g. benzene, at a temperature of 25 °C to 60 °C, within 3 to 24 hours, followed by O-methylation of the hydroxy groups in the C-6, C-11 and C-4'' positions of the intermediate 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-erythromycin A of the formula (II),
wherein

IIb $R^1 = R^2 = CO_2CH_2C_6H_5,$

with a 1-18 molar excess of an appropriate methylation agent, e.g. methyl iodide, dimethyl sulfate, methyl methane sulfonate or methyl *p*-toluenesulfonate, in the presence of an appropriate base, e.g. sodium hydride, aqueous potassium hydroxide or sodium hydroxide, in an appropriate solvent, e.g. dimethyl sulfoxide or N,N-dimethyl-formamide, or their mixtures with a reaction inert solvent, e.g. tetrahydrofurane, acetonitrile, ethyl acetate, 1,2-dimethoxyethane, at a temperature of 0 °C to room temperature, within 3 to 30 hours, yielding a mixture of O-methyl-2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-azithromycin A of the formula (I),
wherein

Ia $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = CH_3, R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = CH_3, R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^5 = H, R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = R^5 = CH_3$

which is optionally subjected to

A) separation on a silica gel column yielding chromatographically homogenous compounds (Ia)-(1d), which are subsequently subjected to the elimination of the protecting groups in positions 2'- and 3'- by means of hydrogenolysis in a solution of lower alcohols, e.g. methanol or ethanol, in the presence of a catalyst, e.g. palladium black or palladium-on-carbon, in a hydrogen atmosphere at a pressure

of 1-20 bar, under stirring of the reaction mixture, within 2-10 hours, at room temperature, yielding O-methyl-N-demethyl-azithromycin A derivatives of formula (I), wherein

Ie $R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$

If $R^1 = R^2 = R^5 = H, R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H, R^4 = CH_3$

Ih $R^1 = R^2 = H, R^3 = R^4 = R^5 = CH_3$

which are then subjected to reductive N-methylation of the 3'-methylamino group with 1-3 equivalents of formaldehyde (37%) and of an equal or double quantity of formic acid (98-100%) or another hydrogen source, in a reaction inert solvent chosen from halogenated hydrocarbons, e.g. chloroform, or lower alcohols, e.g. methanol or ethanol, lower ketones, e.g. acetone, at reflux temperature of the reaction mixture within 2 to 8 hours, yielding O- methylazithromycin A derivatives of formula (I),
wherein

Ii $R^1 = R^4 = R^5 = H, R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H, R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H, R^2 = R^4 = CH_3$

Il $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

or
B) to elimination of the protecting benzyloxycarbonyl group in 2'- and 3'-positions to hydrogenolysis, as described in A), yielding a mixture of O-methyl-azithromycin A derivatives of the formula (I),
wherein

Ii $R^1 = R^4 = R^5 = H, R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H, R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H, R^2 = R^4 = CH_3$

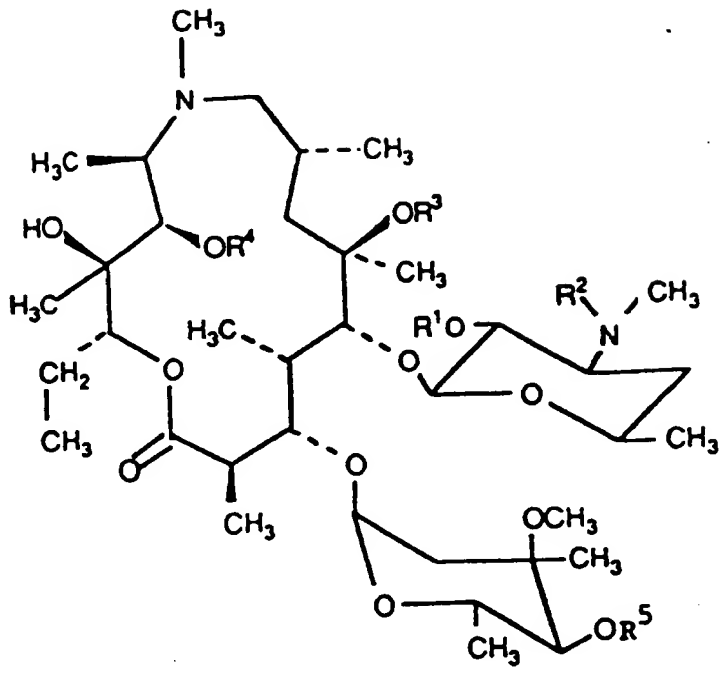
Il $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

which is subjected to separation on a silica gel column yielding chromatographically homogenous O-methyl derivatives of azithromycin A (Ii) - (Il),
which are optionally subjected to reaction with at least one equivalent of an inorganic or organic acid, yielding pharmaceutically acceptable addition salts.

16. Use of O-methyl derivatives of azithromycin A of the formula (I), as claimed in claim 1, in the obtaining of antibacterial pharmaceutical preparations, comprising an antibacterially effective, yet physiologically acceptable amount of said compound of formula (I) and a pharmaceutically acceptable carrier.

Patentansprüche

1. O-Methylderivate von Azithromycin A der Formel (I)



(I)

worin

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

und ihre pharmazeutisch annehmbaren Additionssalze mit anorganischen oder organischen Säuren.

2. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^2 identisch sind und für eine Benzyloxycarbonylgruppe stehen, R^3 die Bedeutung von CH_3 hat, während R^4 und R^5 für Wasserstoff stehen.

3. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^2 identisch sind und für eine Benzyloxycarbonylgruppe stehen, R^3 und R^4 die Bedeutung von CH_3 haben, während R^5 für Wasserstoff steht.

4. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^2 identisch sind und für eine Benzyloxycarbonylgruppe stehen, R^3 und R^5 Wasserstoff sind, während R^4 für CH_3 steht.

5. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^2 identisch sind und für eine Benzyloxycarbonylgruppe stehen, während R^3, R^4 und R^5 die Bedeutung von CH_3 haben.

6. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1, R^2, R^4 und R^5 identisch sind und für Wasserstoff stehen, während R^3 für CH_3 steht.

7. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1, R^2 und R^5 identisch sind und für Wasserstoff stehen, während R^3 und R^4 für CH_3 stehen.

8. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1, R^2, R^3 und R^5 identisch sind und für Wasserstoff stehen, während R^4 für CH_3 steht.

9. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^2 identisch sind und für Wasserstoff stehen, während R^3, R^4 und R^5 für CH_3 stehen.

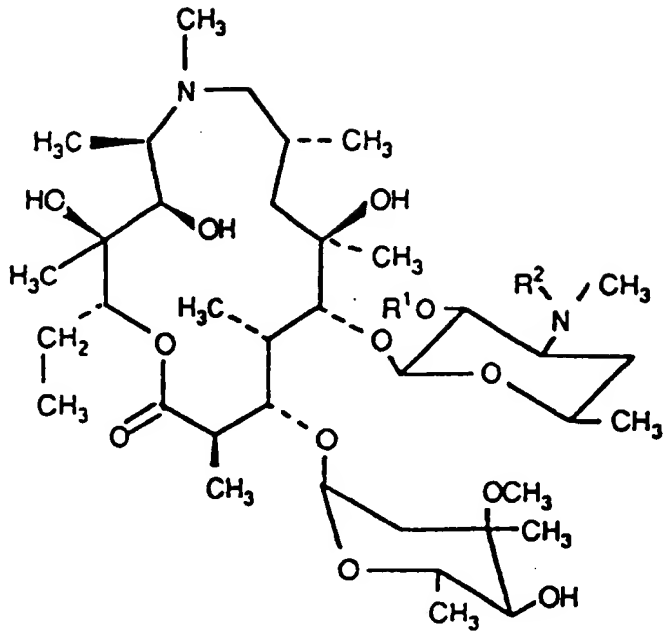
10. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1, R^4 und R^5 identisch sind und für Wasserstoff stehen, während R^2 und R^3 für CH_3 stehen.

11. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 und R^5 identisch sind und für Wasserstoff stehen, während R^2, R^3 und R^4 für CH_3 stehen.

12. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1, R^3 und R^5 identisch sind und für Wasserstoff stehen, während R^2 und R^4 für CH_3 stehen.

13. Substanz gemäss Anspruch 1, *dadurch gekennzeichnet,* dass R^1 für Wasserstoff steht, während R^2, R^3, R^4 und R^5 identisch sind und für CH_3 stehen.

14. Substanz der Formel (II)

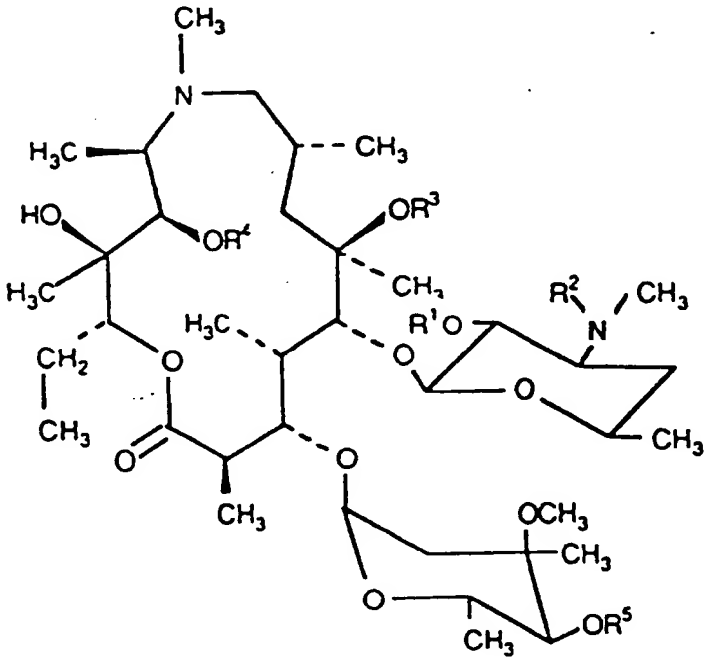


(II)

worin

(IIb) $R^1 = R^2 = CO_2CH_2C_6H_5$.

15. Verfahren zur Herstellung von O-Methylderivaten von Azithromycin A der Formel (I)



(I)

worin

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

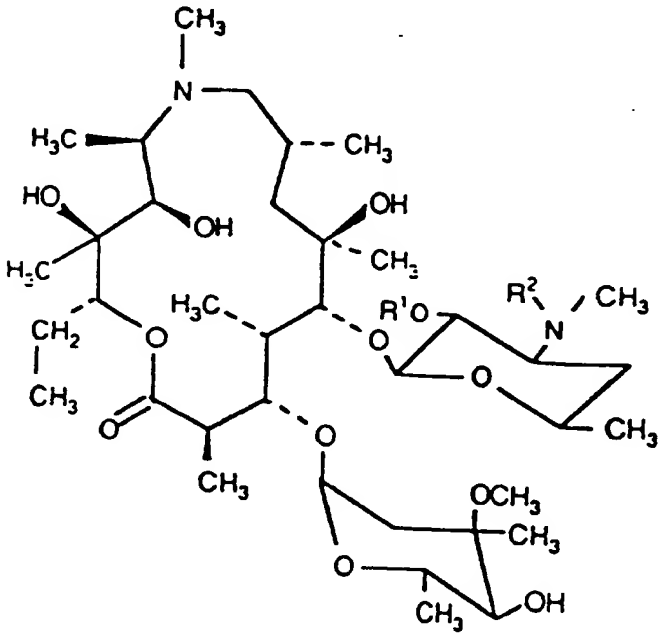
Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

und ihren pharmazeutisch annehmbaren Säureadditionssalzen, *dadurch gekennzeichnet,* dass Azithromycin oder dessen Dihydrat der Formel (II)



(II)

worin

IIa $R^1 = H$, $R^2 = CH_3$,

mit Benzylchloroformiat in Anwesenheit eines Überschusses einer geeigneten Base, z.B. Natriumhydrogencarbonat, in einem reaktionsinerten Lösungsmittel, z.B. Benzol, bei einer Temperatur von 25 °C bis

60 °C innerhalb von 3 bis 24 Stunden umgesetzt wird, anschliessend durch O-Methylierung von Hydroxylgruppen in Stellungen C-6, C-11 und C-4'' der Zwischenverbindung 2'-0,3'-N-Bis-(benzyloxycarbonyl)-N-demethyl-erythromycin A der Formel (II),
worin

IIb $R^1 = R^2 = CO_2CH_2C_6H_5$,

mit einem 1-18-molaren Überschuss eines geeigneten Methylierungsmittels, z.B. Methyliodids, Dimethylsulfats, Methylmethansulfonats oder Methyl-*p*-toluolsulfonats in Anwesenheit einer geeigneten Base, z.B. Natriumhydrids, wässrigen Kaliumhydroxids oder Natriumhydroxids, in einem geeigneten Lösungsmittel, z.B. Dimethylsulfoxid oder N,N-Dimethylformamid oder ihren Mischungen mit einem reaktionsinerten Lösungsmittel, z.B. Tetrahydrofuran, Acetonitril, Ethylacetat, 1,2-Dimethoxyethan, bei einer Temperatur von 0 °C bis Zimmertemperatur innerhalb von 3 bis 30 Stunden umgesetzt wird, wobei eine Mischung von O-Methyl-2'-0,3'-N-bis-(benzyloxycarbonyl)-N-demethyl-azithromycin A der Formel (I),
worin

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

erhalten wird, die gegebenenfalls

A) einer Trennung an einer Silikagelsäule unterworfen wird, so dass chromatographisch homogene Verbindungen (Ia)-(Id) erhalten werden, die anschliessend der Abspaltung der Schutzgruppen in Stellungen 2'- und 3'- mittels Hydrogenolyse in einer Lösung von niedrigeren Alkoholen, z.B. Methanol oder Ethanol, in Anwesenheit von einem Katalysator, z.B. Palladiumschwarz oder Palladium an Kohle, in Wasserstoffatmosphäre bei einem Druck von 1-20 bar, unter Rühren der Reaktionsmischung innerhalb von 2 bis 10 Stunden bei Zimmertemperatur unterworfen werden, wobei O-Methyl-N-demethyl-Derivate von Azithromycin A,
worin

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

erhalten werden,

die anschliessend einer reduktiven N-Methylierung der 3'-Methylaminogruppe mit 1-3 Äquivalenten von Formaldehyd (37%) und einer gleichen oder doppelten Menge von Ameisensäure (89-100%) oder einer anderen Wasserstoffquelle in einem reaktionsinerten Lösungsmittel, gewählt aus halogenierten Kohlenwasserstoffen, z.B. Chloroform, oder niedrigen Alkoholen, z.B. Methanol oder Ethanol, niedrigen Ketonen, z.B. Aceton, bei Rückflusstemperatur der Reaktionsmischung innerhalb von 2 bis 8 Stunden unterworfen werden, so dass O-Methylderivate des Azithromycins A der Formel (I),
worin

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

II $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

erhalten werden,
oder

B) einer Abspaltung der Benzyloxycarbonylschutzgruppe in Stellungen 2'- und 3'- mittels Hydrogenolyse wie in A) beschrieben ist, unterworfen wird, wobei eine Mischung von O-Methylderivaten von Azithromycin A der Formel (I),
worin

Ii $R^1 = R^4 = R^5 = H, R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H, R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H, R^2 = R^4 = CH_3$

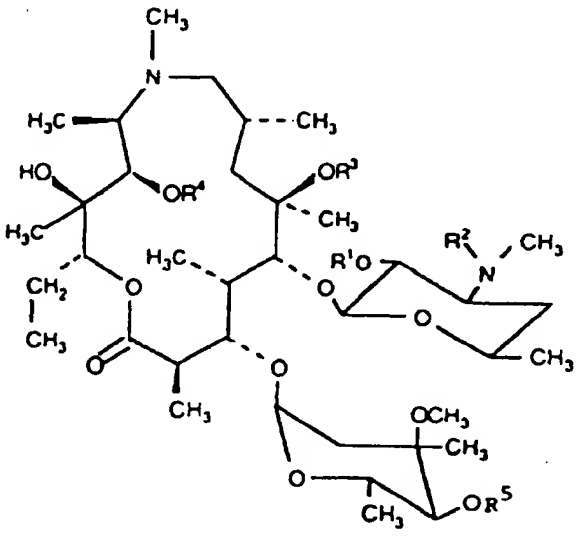
II $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

erhalten wird,
die einer Trennung an Silikagelsäule unterworfen wird, so dass chromatographisch homogene O-Methylderivate von Azithromycin A (Ii)-(II) gewonnen werden, die gegebenfalls der Reaktion mit wenigstens einem Äquivalenten einer anorganischen oder organischen Säure unterworfen werden, wobei pharmazeutisch annehmbare Additionssalze gewonnen werden.

16. Verwendung von O-Methylderivaten von Azithromycin A der Formel (I) gemäss Anspruch 1 bei der Herstellung von antibakteriellen pharmazeutischen Zubereitungen enthaltend eine antibakteriell wirksame, jedoch physiologisch annehmbare Menge der genannten Verbindung der Formel (I) und einen pharmazeutisch annehmbaren Träger.

Revendications

1. Dérivé O-méthylé de l'azithromycine A de la formule (I)



(I)

dans laquelle

Ia $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = CH_3, R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = CH_3, R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

et leurs sels d'addition obtenus avec des acides minéraux ou organiques, acceptables sur le plan pharmaceutique.

2. Substance selon la revendication 1, caractérisée en ce que R^1 et R^2 sont identiques et représentent chacun un groupe benzyloxycarbonyle, R^3 est un CH_3, alors que R^4 et R^5 représentent chacun un hydrogène.

3. Substance selon la revendication 1, caractérisée en ce que R^1 et R^2 sont identiques et représentent chacun un groupe benzyloxycarbonyle, R^3 et R^4 sont chacun un CH_3, alors que R^5 représente un hydrogène.

4. Substance selon la revendication 1, caractérisée en ce que R^1 et R^2 sont identiques et représentent chacun un groupe benzyloxycarbonyle, R^3 et R^5 sont chacun un hydrogène, alors que R^4 représente un CH_3.

5. Substance selon la revendication 1, caractérisée en ce que R^1 et R^2 sont identiques et représentent chacun un groupe benzyloxycarbonyle, alors que R^3, R^4 et R^5 sont chacun un CH_3.

6. Substance selon la revendication 1, caractérisée en ce que R^1, R^2, R^4 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^3 représente un CH_3.

7. Substance selon la revendication 1, caractérisée en ce que R^1, R^2 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^3 et R^4 représentent chacun un CH_3.

8. Substance selon la revendication 1, caractérisée en ce que R^1, R^2, R^3 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^4 représente un CH_3.

9. Substance selon la revendication 1, caractérisée en ce que R^1 et R^2 sont identiques et représentent chacun un hydrogène, alors que R^3, R^4 et R^5 représentent chacun un CH_3.

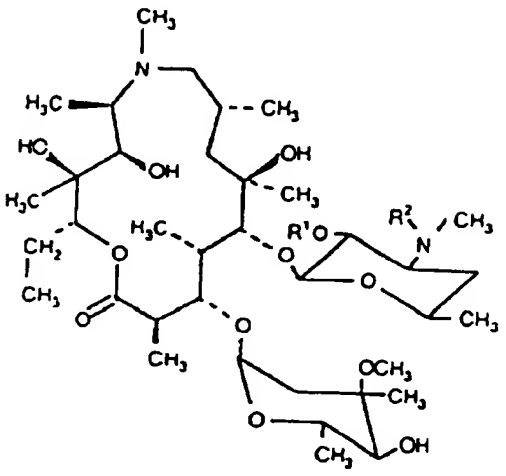
10. Substance selon la revendication 1, caractérisée en ce que R^1, R^4 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^2 et R^3 représentent un CH_3.

11. Substance selon la revendication 1, caractérisée en ce que R^1 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^2, R^3 et R^4 représentent chacun un CH_3.

12. Substance selon la revendication 1, caractérisée en ce que R^1, R^3 et R^5 sont identiques et représentent chacun un hydrogène, alors que R^2 et R^4 représentent chacun un CH_3.

13. Substance selon la revendication 1, caractérisée en ce que R^1 représente un hydrogène, alors que R^2, R^3, R^4 et R^5 sont identiques et représentent chacun un CH_3.

14. Substance selon la formule (II)

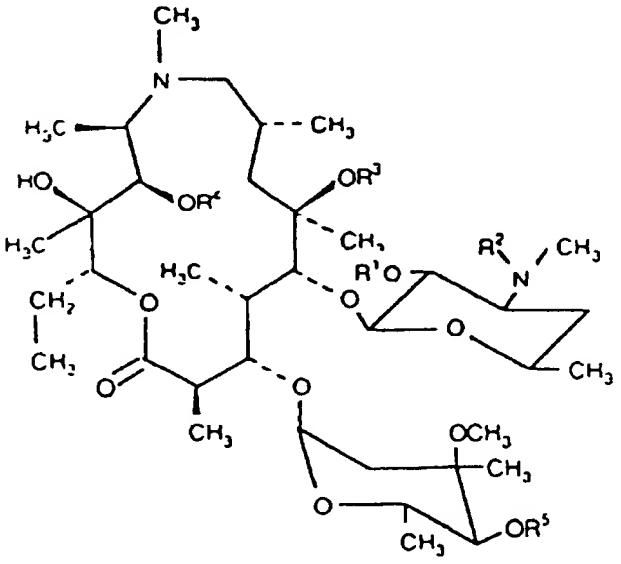


(II)

dans laquelle

(IIb) $R^1 = R^2 = CO_2CH_2C_6H_5$.

15. Procédé pour la préparation de dérivés O-méthylés de l'azithromycine A de la formule (I)



(I)

dans laquelle

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^{5'} = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5, R^3 = R^4 = R^5 = CH_3$

Ie $R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$

If $R^1 = R^2 = R^5 = H, R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H, R^4 = CH_3$

Ih $R^1 = R^2 = H, R^3 = R^4 = R^5 = CH_3$

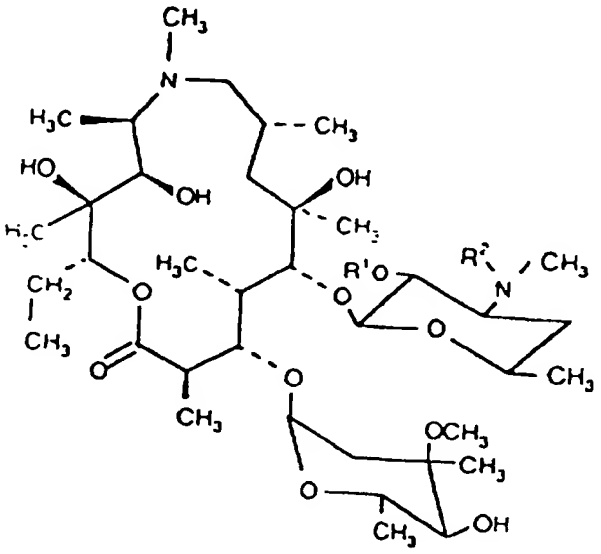
Ii $R^1 = R^4 = R^5 = H, R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H, R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H, R^2 = R^4 = CH_3$

Il $R^1 = H, R^2 = R^3 = R^4 = R^5 = CH_3$

et leurs sels d'addition obtenus avec des acides, acceptables sur le plan pharmaceutique, caractérisé en ce qu'on fait réagir l'azithromycine ou son dihydrate de la formule (II)



(II)

dans laquelle

IIa $R^1 = H, R^2 = CH_3,$

avec du chloroformiate de benzyle en présence d'un excès d'une base appropriée, par exemple de carbonate acide de sodium, dans un solvant de réaction inerte, par exemple le benzène, à une température de 25 °C à 60 °C pendant 3 à 24 heures, cette réaction étant suivie par une O-méthylation des groupes hydroxy en position C-6, C-11 et C-4'' de l'intermédiaire 2'-0,3'-N-bis-(benzyloxycarbonyl)-N-déméthyl-érythromycine A de la formule (II),
dans laquelle

IIB $R^1 = R^2 = CO_2CH_2C_6H_5,$

avec un excès 1-18 molaire d'un agent de méthylation approprié, par exemple l'iodure de méthyle, le diméthyle sulfate, le méthyle méthane sulfonate ou le méthyle *p*-toluènesulfonate, en présence d'une base appropriée, par exemple l'hydrure de sodium, l'hydroxyde de potassium ou l'hydroxyde de

sodium aqueux, dans un solvant approprié, tel que le diméthyle sulfoxyde ou le N,N-diméthylformamide, ou leurs mélanges avec un solvant inerte tel que le tétrahydrofurane, l'acétonitrile, l'acétate d'éthyle, le 1,2-diméthoxyéthane, à une température dans la plage allant de 0 °C à la température ambiante, pendant 3 à 30 heures, pour donner un mélange de O-méthyl-2'-0,3'-N-bis-(benzyloxycarbonyl)-N-déméthyl-azithromycine A de la formule (I)
dans laquelle

Ia $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = CH_3$, $R^4 = R^5 = H$

Ib $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$

Ic $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^5 = H$, $R^4 = CH_3$

Id $R^1 = R^2 = CO_2CH_2C_6H_5$, $R^3 = R^4 = R^5 = CH_3$

qui est éventuellement soumis à

A) une séparation sur une colonne de gel de silice pour donner des composés (Ia) - (Id) homogènes en chromatographie, qui sont ensuite soumis à l'élimination des groupes protecteurs dans les positions 2'- et 3'-au moyen d'une hydrogénolyse dans une solution d'un alcool inférieur, par exemple le méthanol ou l'éthanol, en présence d'un catalyseur, par exemple le noir de palladium ou le palladium sur charbon, sous une atmosphère d'hydrogène à une pression de 1-20 bar, sous agitation du mélange réactionnel, pendant 2-10 heures, à température ambiante, pour donner des dérivés O-méthyl-N-déméthyl-azithromycine A de la formule
(I), dans laquelle

Ie $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$

If $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = CH_3$

Ig $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$

Ih $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = CH_3$

qui sont alors soumis à une N-méthylation réductrice de groupe 3'-méthylamino avec 1-3 équivalents de formaldéhyde (37%) et une quantité égale ou double d'acide formique (98-100%) ou d'une autre source d'hydrogène, dans un solvant inerte de réaction choisi parmi les hydrocarbures halogénés comme le chloroforme ou les alcools inférieurs comme le méthanol ou l'éthanol, les cétones inférieures comme l'acétone, à la température du reflux du mélange réactionnel pendant 2 à 8 heures, pour donner les dérivés O-méthylazithromycine A de la formule (I),
dans laquelle

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

ou

B) une élimination du groupe protecteur benzyloxycarbonyle en positions 2'- et 3'-. par hydrogénolyse comme décrit en A), pour donner un mélange de dérivés O-méthyl-azithromycine A de la formule (I)
dans laquelle

Ii $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$

Ij $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$

Ik $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$

Il $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = CH_3$

qui est soumis à une séparation sur une colonne de gel de silice pour donner les dérivés O-méthylés de l'azithromycine A (Ii) - (Il) homogènes en chromatographie,
qui sont éventuellement soumis à une réaction avec au moins un équivalent d'un acide minéral ou organique, pour donner des sels d'addition acceptables sur la plan pharmaceutique.

16. Utilisation de dérivés O-méthylés de l'azithromycine A de la formule (I) selon la revendication 1, pour l'obtention de préparations pharmaceutiques antibactériennes comprenant une quantité suffisante de dérivé de la formule (I) pour avoir un effet antibactérien tout en restant acceptable sur le plan physiologique, et un vecteur acceptable sur le plan pharmaceutique.